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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RIGGINS, PATRICK S	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/633,699	UMANA ET AL.	
	Examiner	Art Unit	
	Patrick S. Riggins	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2003 and 22 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86-108* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

1. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

2. The disclosure is objected to because of the following informalities: Sequences have been disclosed and there is not full compliance with sequence rules. See 37 C.F.R. 1.821-1825. Specifically, sequences are disclosed in Figures 7 and 8, yet there is no reference to the sequence list. Identifying the appropriate SEQ ID NOs in the Brief Description of Drawings would be remedial. The following errors in the specification are also noted:

a. on page 6, line 11 it is recited "TnT, GlcNAc transferase" in reference to figure 11, while it would appear this was intended to recite --GnT, GlcNAc transferase--

b. on page 6, lines 24-25 the lanes of figure 13 are improperly labeled. This should recite --2000ng/ml(Lane B), 50ng/ml(Lane C), and 25ng/ml(Lane D)--

c. there are numerous improper usages of Trademarked names as follows:

i. page 32, line 30 Tween 20

ii. page 33, line 12 SepPak

iii. page 33, line 13 Dowex

iv. page 33, line 15 Gel Loader Tip

v. page 34, line 9, Triton X-100.

They should be capitalized wherever they appear and be accompanied by generic terminology. Although the use of trademarks is permissible in patent applications,

the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction of all above issues is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 87 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

5. Claim 87 is drawn to a glycoengineered antibody with modified glycosylation patterns that results in an increased binding affinity for Fc receptors. The specification has not sufficiently taught how to make this antibody, as no evidence has been provided that enhanced Fc receptor binding is the mechanism of the enhanced antibody-mediated cell death that is observed.

6. A number of factors have been considered in making this assertion that undue experimentation is required to practice this invention as delineated by *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in

the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

7. Claim 87 is broadly drawn as it reads on any recombinant antibody with an altered glycosylation pattern in its Fc region. This antibody must bind with greater affinity to Fc receptors. The specification teaches that altering the N-glycosylation pattern on an antibody molecule can lead to enhance antibody-mediated cell killing. The specification defines Fc-mediated cellular cytotoxicity as antibody-dependent cellular cytotoxicity, which is known to occur through engagement of low-affinity Fc receptors on the surface of granular cells, leading to the degranulation of those cells, and subsequent cell killing. The specification provides no evidence that the modifications to antibody molecules leads to higher affinity of those modified antibodies for Fc receptors. Additionally, the section of the specification that attempts to address this issue states, "Modification of the oligosaccharide structure can therefore be explored as a means to increase the affinity of the interaction [with Fc receptors]" (emphasis added)(page 21, lines 24-25). This is a statement that essentially outright states that additional experimentation would be required to ensure that a modified antibody had an increase in Fc receptor affinity.

8. Another possible explanation for the increase in antibody-mediated cellular cytotoxicity that is observed is that the glycosylation modifications made to the antibodies could instead lead to enhanced complement-mediated cell lysis. Indeed, Lund teaches that altered glycosylation patterns on antibodies can indeed lead to differential ability to fix complement (see Figure 1-3). Though the assays for measuring Fc-mediated cell lysis were set up to measure a cell-mediated mechanism, the assays were performed in serum, which contains the components of

complement. Thus the inventors have not provided sufficient evidence as to the mechanism of Fc-mediated cellular cytotoxicity. Absent a teaching as to the specific mechanism, the disclosure does not provide sufficient instruction to the skilled artisan of how to reliably and definitively make an antibody that has an increased affinity for Fc receptors. Therefore the specification is not enabling for claim 87.

9. Claims 88-107 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for production of antibodies with increases Fc-mediated cellular cytotoxicity, does not reasonably provide enablement for antibodies with an increases affinity for Fc receptors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

10. Claims 88-107 all ultimately depend from claim 86 or claim 87. As described above, claim 87 is rejected on the grounds that the specification is not enabling for production of antibodies with increased affinity for Fc receptors. As claims 88-107 all in part depend from claim 86 or 87, and as such must contain all the limitations of either claim 86, such that the antibodies all have increased Fc-mediated cellular cytotoxicity, or claim 87, such that the antibodies they all define must have an increase in affinity for Fc receptors. As described above, the specification provides sufficient disclosure to enable the skilled artisan to make antibodies with increased Fc-mediated cellular cytotoxicity. Also as described above, the specification does not enable the killed artisan to make antibodies with increased Fc receptor affinity. Thus, the specification is not enabling for the complete scope of claims 88-107.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 86-102, and 104-108 are rejected under 35 U.S.C. 102(b) as being anticipated by Lifely (of record). These claims are all drawn to recombinant antibody with altered glycosylation patterns, optionally as a chimeric antibody, a humanized antibody, an Fc-containing antibody fragment, an Fc-containing fusion protein, a therapeutic antibody, a cancer antigen-binding antibody, a monoclonal antibody, or an IgG. The glycosylation can optionally have an increased proportion of GlcNAc residues, a decreased proportion of fucose residues, consist of bisected oligosaccharides, or be non-fucosylated. Lifely, through the use of different cell lines, produced CAMPATH-1H antibodies with altered glycosylation patterns (see predominantly figures 1, 4, and 5, and Table III).

13. Indeed CAMPATH-1H is a humanized IgG, which by definition is chimeric, and the glycosylation-modified antibodies produced in the Y0 cells possess enhanced Fc-mediated cellular cytotoxicity (Figure 5) and would inherently possess any increase in Fc receptor affinity. The claims are all product by process claims, and as stated in Chapter 2113 of the MPEP "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made

by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)" In the instant case, the antibodies produced by Lifely appear to be substantially he same as the antibodies produced in the glycoengineering protocols of the instant application.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 86-108 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lifely in view of Reff (of record), Amstutz (of record), Luiten, Valone, Kaszubowski, Murakami, Mordoh (U.S. Patent No. 5,753,229), Shoemaker (U.S. Patent No. 4,978,745), Chapman (U.S. Patent No. 5,529,922), and De Bree. Lifely teaches of antibodies with altered glycosylation patterns that have increased Fc-mediated cellular cytotoxicity, would inherently possess any increases affinity for Fc receptors, and are therapeutic antibodies. Lifely does not disclose the specific antibodies listed in claim 103. An antibody against CD20, against human neuroblastoma, against human renal cell carcinoma, HER-2, against human colon cancer, against human lung cancer, against human breast cancer, human 17-1A antibody that is a humanized anticolorectal tumor antibody, against human melanoma, and against human squamous-cell carcinoma are taught by Reff, Amstutz, Luiten, Valone, Kaszubowski, Murakami, Mordoh, Shoemaker, Chapman, and De Bree, respectively. One can find motivation for producing these antibodies with a modified glycosylation pattern, on the first page of Lund: "Glycosylation of IgG Ab molecules at Asn^{297}

has been shown consistently to be a requirement for optimal recognition and activation of effector mechanism through FcγR and the C1 component of [complement]."

16. Thus, as it was known in the art that glycosylation is important for these activities, the skilled artisan would have been motivated to enhance the ability of antibodies to mediate their effector functions. The modifications of Lifely provide that ability. Thus, one would have had a high likelihood of success in creating antibodies with enhanced activity using the antibodies of Reff et al. in the production methods of Lifely. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Lifely with the antibodies taught, by Reff, Amstutz, Luiten, Valone, Kaszubowski, Murakami, Mordoh, Shoemaker, Chapman, and De Bree.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 86, 87, 93, 96, and 108 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 113-116 and 256-258 of copending Application No. 10/981,837, as follows: instant claims 86 and 108 over

reference claims 113, 116, and 256, instant claim 87 over reference claims 114, 114, and 256, instant claim 93 over reference claim 258, and instant claim 96 over reference claim 257. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). Although the conflicting claims are not identical, they are not patentably distinct from each other because, in the case of instant claims 86, 87, 93, 96, and 108, they are generic to all that is recited in the respective claims of the reference, i.e. the reference claims fall entirely within the scope of each of instant claims 86, 87, 93, 96, and 108.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

19. Claims 86, 87, 90, 91, and 108 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 96-98, 108-111, 213, 261-263, and 273-276 and 256-258 of copending Application No. 10/761,435, as follows: instant claims 86 and 108 over reference claims 96, 98, 213, 261, and 263, instant claim 87 over reference claims 96-97, 213, and 261-262, instant claim 90 over reference claims 108, 110, 273, and 275, and instant claim 91 over reference claims 109, 111, 274, and 276. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). Although the conflicting claims are not identical, they are not patentably distinct from each other because, in the case of instant claims 86, 87, 90, 91, and 108, they are generic to all that is recited

in the respective claims of the reference, i.e. the reference claims fall entirely within the scope of each of instant claims 86, 87, 90, 91, and 108.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claims 86, 90, 91, 103, and 108 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 74-85 of copending Application No. 10/633, 697, as follows: instant claims 86 and 108 over reference claims 74-83, instant claim 90 over reference claim 84, instant claim 91 over reference claim 85, and instant claim 103 over reference claims 75-83. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). Although the conflicting claims are not identical, they are not patentably distinct from each other because, in the case of instant claims 86, 90, 91, 103, and 108, they are generic to all that is recited in the respective claims of the reference, i.e. the reference claims fall entirely within the scope of each of instant claims 86, 90, 91, 103, and 108.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

21. Claims 86 and 108 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 127 of copending Application No. 10/437,388. Although the conflicting claims are not identical, they are not patentably distinct from each other because, an obviousness-type double patenting rejection is

appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, there reference claim(s). Chapter 804 of the MPEP states,

> [t]he specification can always be used as a dictionary to learn the meaning of a term in the patent [reference] claim. In re Boylan, 392 F.2d 1017, 157 USPQ 370 (CCPA 1968). Further, those portions of the specification which provide support for the patent [reference] claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent [reference]. In re Vogel, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in Vogel recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent [reference] which provides support for the patent [reference] claim. According to the court, one must first "determine how much of the patent [reference] disclosure pertains to the invention claimed in the patent [reference]" because only "[t]his portion of the specification supports the patent [reference] claims and may be considered." The court pointed out that "this use of the disclosure in not in contravention of the cases forbidding its use as prior art, nor is it applying the patent [reference] as a reference under 35 U.S.C 103, since only the disclosure of the invention claimed in the patent [reference] may be examined."

The instant claims 86 and 108 are more narrowly drawn than reference claim 127. However, as the instant application and the reference application are both continuations of application number 09/294,584 they necessarily share the same specification. Thus the reference application necessarily teaches the additional limitation of increase Fc-mediated cellular cytotoxicity found in instant claims 127. Thus, instant claims 86 and 108 are not patentably distinct from reference claim 127.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

22. Claims 86, 90, 91, 103, and 108 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 28-31 of copending Application No. 10/211,554, as follows: instant claims 86 and 108 over reference claims 28 and 29, instant claim 90 over reference claim 30, instant claim 91 over reference claim 31, and instant claim 103 over reference claim 29. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). Although the conflicting claims are not identical, they are not patentably distinct from each other because, in the case of instant claims 86, 90, 91, 103, and 108, they are generic to all that is recited in the respective claims of the reference, i.e. the reference claims fall entirely within the scope of each of instant claims 86, 90, 91, 103, and 108.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick S. Riggins whose telephone number is (571) 272-6102. The examiner can normally be reached on M-F 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick Riggins, Ph.D.
Examiner
Art Unit 1636

JAMES KETTER
PRIMARY EXAMINER